Medical Officer Comment: Two of the patients with respiratory tract infections were considered failures in the clinical outcome evaluation, including the patient diagnosed with pneumonia (#4 00003, #18 00002).

8.1.4.2.2.2 RELAPSES: There were no relapses in this study.

8.1.4.2.2.3 RESISTANCE ISSUES:
None of the baseline isolates were resistant to gatifloxacin. None of the pathogens which were isolated at the end of the treatment period were resistant to gatifloxacin.

8.1.4.2.2.4 ATYPICAL PNEUMONIA:
Only one case of C. pneumoniae was documented by serology.

Medial Officer Comment: Review of the SAS transport file revealed two clinically evaluable patients who were diagnosed as having C. pneumoniae, both were clinical cures. However, this small number of patients does not add much to the previous documentation of activity of gatifloxacin against C. pneumoniae.

8.1.4.3 SAFETY RESULTS:
8.1.4.3.1 Overall and Related Adverse Clinical Events:
Gatifloxacin was well tolerated in the 150 patients treated. Overall, ninety-seven (65%) patients experienced one or more adverse clinical events. The most common adverse clinical events were abnormal breath sounds (13%), dyspnea (11%), headache (11%), vaginitis (10%) and nausea (9%).

Adverse Clinical Events of All Causes, by Relationship to Study Drug, All Treated Patients
Protocol AI420-003

	Number (%) of Patients N = 150							
Adverse Clinical Event[a]	Related		Not Related		Unassessed		Total	
Any Adverse Clinical Event	61	(41)	34	(23)	2	(1)	97	(65)
Abnormal Breath Sounds	3	(2)	14	(9)	2	(1)	19	(13)
Headache	9	(6)	8	(5)	-		17	(11)
Dyspnea	3	(2)	12	(8)	1	(<1)	16	(11)
Vaginitis[b]	7	(9)	-		1	(<1)	8	(10)
Nausea	12	(8)	2	(1)	-		14	(9)
Coughing	2	(1)	10	(7)	-		12	(8)
Pain	2	(1)	9	(6)	-		11	(7)
Abdominal Pain	7	(5)	2	(1)	1	(<1)	10	(7)
Sputum Increased	1	(<1)	8	(5)	-		9	(6)
Diarrhea	7	(5)	-		-		7	(5)
Dry Mouth	7	(5)	-		-		7	(5)
Malaise	5	(3)	2	(1)	-		7	(5)
Rash	5	(3)	1	(<1)	1	(<1)	7	(5)
Vomiting	5	(3)	2	(1)	-		7	(5)
Chest Pain	-		7	(5)	-		7	(5)
Dyspepsia	5	(3)	-		-		5	(3)
Pruritus	5	(3)	-		-		5	(3)
Taste Perversion	5	(3)	-		-		5	(3)
Asthenia	4	(3)	1	(<1)	-		5	(3)
Abnormal Vision	4	(3)	1	(<1)	-		5	(3)
Pneumonia	-		5	(3)	-		5	(3)
Insomnia	4	(3)	-		-		4	(3)
Dizziness	3	(2)	1	(<1)	-		4	(3)
Asthma	1	(<1)	3	(2)	-		4	(3)
Anorexia	3	(2)	-		-		3	(2)
Somnolence	3	(2)	-		-		3	(2)
Constipation	2	(1)	1	(<1)	-		3	(2)
Sweating	1	(<1)	2	(1)	-		3	(2)

[a] All adverse events occurring in ≥2% of the total number of treated patients.

[b] Based on 81 women.

(Reference: Vol. 8, p. 79)

Medical Officer Comment: None of the patients reported pancreatitis, tendon rupture, phototoxicity, or seizures as adverse events during this study. Five patients had adverse events categorized as cardiovascular while on medication. One patient had a myocardial

infarction and atrial fibrillation (she subsequently died of nosocomial pneumonia), another had cardiac failure and palpitations, one had carotid bruit, another had palpitations and the last patient had an arrhythmia with underlying cardiovascular disease history. None of these were considered by the clinicians to be related to the study drug. There was one patient reported to have suffered a seizure. This patient had a past history of seizures as a child, not on any medications for seizures and willing to tolerate occasional breakthrough seizures. He did not suffer any adverse events from this seizure.

Adverse Clinical Events Related to Study Drug

Sixty-one (41%) patients had adverse events considered related to gatifloxacin, of which fifty-four (90%) were considered mild to moderate in nature of severity. The most common drug related adverse events were vaginitis (9%), nausea (8%), headache (6%), diarrhea (5%), abdominal pain (5%), and dry mouth (5%).

Drug Related Adverse Clinical Events, by Severity
All Treated Patients,
Protocol AI420-003

	Number (%) of Patients N = 150									
Adverse Clinical Event	Mild		Moderate		Severe		Very Severe		Total	
Any Related Adverse Clinical Event	33	(22)	21	(14)	7	(5)	-		61	(41)
Vaginitis[b]	3	(4)	4	(5)	-		-		7	(9)
Nausea	10	(7)	-		2	(1)	-		12	(8)
Headache	4	(3)	4	(3)	1	(<1)	-		9	(6)
Abdominal Pain	5	(3)	2	(1)	-		-		7	(5)
Dry Mouth	3	(2)	1	(<1)	3	(2)	-		7	(5)
Diarrhea	5	(3)	2	(1)	-		-		7	(5)
Dyspepsia	3	(2)	2	(1)	-		-		5	(3)
Vomiting	4	(3)	-		1	(<1)	-		5	(3)
Taste Perversion	2	(1)	1	(<1)	2	(1)	-		5	(3)
Rash	3	(2)	1	(<1)	1	(<1)	-		5	(3)
Malaise	5	(3)	-		-		-		5	(3)
Pruritus	2	(1)	2	(1)	1	(<1)	-		5	(3)
Abnormal Vision	4	(3)	-		-		-		4	(3)
Insomnia	1	(<1)	3	(2)	-		-		4	(3)
Asthenia	3	(2)	1	(<1)	-		-		4	(3)
Somnolence	2	(1)	1	(<1)	-		-		3	(2)
Anorexia	3	(2)	-		-		-		3	(2)
Dizziness	3	(2)	-		-		-		3	(2)
Abnormal Breath Sounds	3	(2)	-		-		-		3	(2)
Dyspnea	1	(<1)	2	(1)	-		-		3	(2)
Coughing	1	(<1)	1	(<1)	-		-		2	(1)
Stomatitis	2	(1)	-		-		-		2	(1)
Paresthesia	1	(<1)	-		1	(<1)	-		2	(1)
Hallucination	1	(<1)	1	(<1)	-		-		2	(1)
Constipation	2	(1)	-		-		-		2	(1)
Eye Pain	2	(1)	-		-		-		2	(1)
Pain	1	(<1)	1	(<1)	-		-		2	(1)

a Occurring in ≥1% of the patients.

b Based on 81 women.

(Reference: Vol. 8, p. 81)

Medical Officer Comment: Theses rates are similar to those seen in the NDA database.

8.1.4.3.2 Discontinuations Due to Adverse Clinical Events:

There were eight (5%) patients discontinued due to adverse events. There were no study drug discontinuations due to laboratory abnormalities.

Discontinuation of Study Medication Due to Adverse Clinical Events, All Treated Patients
Protocol AI420-003

Patient Number	Adverse Clinical Event	Relationship to Gatifloxacin	Duration of Dosing (Days)	Onset of Adverse Clinical Event (Study Day)
048-003	Gastroenteritis	Not related	1	1
037-001	Nausea, visual hallucinations	Probably Related	3	1
023-008	Skin rash, pruritus, nausea, vomiting, flushing, dizziness and sweating	Related	2	1
032-016	Abdominal pain, rectal hemorrhage	Possibly Related	7	1
032-025	Nausea, vaginal pruritus	Probably Related	7	4
041-002	Myocardial infarction, atrial fibrillation	Not Related	8	8
052-001	Urticaria of the wrists, total body pruritus	Probably Related	13	9
053-006	Worsening cough and dyspnea increased sputum production, chest tightness, respiratory disuress and lung carcinoma	Not Related	9	9

(Reference: Vol. 8, p. 84)

8.1.4.3.3 Serious Adverse Events and Deaths:

Eight patients experienced serious adverse events (SAE) on study, none of which were attributed to study therapy. Two patients required hospitalization for pneumonia after three days of therapy with gatifloxacin. One patient with epilepsy experienced "seizure-like movement" the first day of gatifloxacin therapy. Cardiac arrhythmia, myocardial infarction and palpitations, requiring hospitalization, were SAEs experienced once by three patients. Another patient was hospitalized with acute gastroenteritis after one day of study treatment, and the last patient was found to have a right lower lobe bronchial neoplasm requiring hospitalization 9 days after study therapy.

Serious Adverse Clinical Events of All Causes, All Treated Patients Protocol AI420-003

	Number of Patients
Serious Adverse Clinical Event[a]	N = 150
Any Serious Adverse Clinical Event	14
Patients with Serious Adverse Clinical Events	8
Pneumonia	4
Dyspnea	2
Gastroenteritis	1
Neoplasm	1
Pain Chest	1
Arrhythmia	1
Atrial Fibrillation	1
Myocardial Infarction	1
Palpitation	1
Convulsion	1

[a] Patients may have more than one serious adverse clinical event.
(Reference: Vol. 8, p. 83)

The following briefly summarizes these serious adverse events:

- **Patient, 009-012**, went to the emergency room on Day 1 because his roommate reported that he had a seizure-like movement. He had a 20 year history of 1-2 seizures per year. The patient completed the 14 day regimen of gatifloxacin treatment without any further incidence of seizure-like activity and was clinically cured of a documented *M. catarrhalis* pneumonia. This patient was not treated with any anti-seizure medications.

- **Patient, 009-013**, discontinued study therapy on Day 3 when he developed increased chest pain. He was hospitalized for exacerbation of pneumonia and treated with ceftriaxone (IV) for 3 days. This patient was discharged after three days.

- **Patient, 016-005**, was hospitalized on Day 8 when he developed cardiac arrhythmia. He was hospitalized for seven days without any specific treatment for this event. This patient completed gatifloxacin treatment.

- **Patient, 032-006**, discontinued study therapy on Day 3 when she developed worsening dyspnea. She was hospitalized for exacerbation of pneumonia and treated with ceftriaxone (IV) for 3 days. This patient was discharged home after 14 days.

- **Patient, 040-003**, was hospitalized on Day 9 when she developed palpitations and worsening dyspnea. She was hospitalized for five days without any specific treatment for these events. This patient finished gatifloxacin treatment.

- **Patient, 041-002,** discontinued study therapy on Day 8 when she developed atrial fibrillation and experienced a myocardial infarction. She was hospitalized and subsequently developed a nosocomial pneumonia for which she was treated with [redacted] clindamycin, ceftazidime, ceftriaxone and erythromycin. The patient expired due to cardiac failure on Day +15.

- **Patient, 048-003,** discontinued study therapy on Day 1 when she developed acute gastroenteritis and was unable to take oral medication. She was hospitalized and treated with ceftriaxone and [redacted] On Day 4, the investigator felt that the hospitalization was prolonged due to the pneumonia. This patient was discharged with a good clinical outcome after 14 days.

- **Patient, 053-006,** discontinued study therapy on Day 9 when he developed respiratory distress. He was hospitalized on Day 9 and found to have a poorly differentiated squamous cell carcinoma located in the right main bronchus. Treatment consisted of cefazolin, amoxicillin/clavulanic acid, albuterol and ipratropium. Hospital discharge occurred after 8 days.

Medical Officer Comment: The patient with reported to have had a seizure on the first day of study medication had a history of seizures. This may have been do to the drug; however, the patient had a predisposing condition. The patient completed the study medication without further seizure activity.

Deaths:
One patient died due to cardiac failure. This death was not considered to be related to study drug.

8.1.4.3.4 Additional Safety Considerations

Patient, 032-012, had a positive β-HCG urine pregnancy test on Day +33. She had a negative pre-treatment pregnancy test in compliance with the protocol. The estimated gestational age at this time was 4 weeks. This woman's method of contraception was condom use. A full 14 days of gatifloxacin was administered to this patient. The patient decided to terminate the pregnancy and underwent an induced abortion.

8.1.4.3.5 Laboratory Abnormalities:

Abnormal Laboratory Test Values During or Post-treatment in Patients with Normal Pre-treatment Values

In general, the development of abnormal laboratory test values during or post-treatment in patients with normal pre-treatment values was uncommon; most that did occur were mild (Grade 1). There were eighteen Grade 2 laboratory abnormalities. The most frequent abnormalities were elevated ALT (14%), and elevated AST (12%).

Three patients with normal baseline values experienced a Grade 3 or 4 toxicity. Patient, 027-001, had an elevated creatinine of 10mg/dL, (Grade 4), on Day +8. This patient's previous creatinine levels on Day 1 and Day 5 were within the normal range. Serum was redrawn on Day +16 and the creatinine level was found to be normal. There was no apparent reason for this isolated elevated creatinine value. Patient, 032-012, had an elevated potassium of 8.5mEq/L, Grade 4, on Day +19. This patient's previous potassium levels both pre-treatment and during therapy were within the normal range and this patient did not experience any adverse clinical events. The investigator felt that this

abnormal value was because of sample hemolysis. Patient, 032-006, had decreased chloride level of 88 mEq/L (baseline 96mEq/L, Grade 3), on Day +1. No further follow-up values were obtained.

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Abnormal Laboratory Test Values During or Post-treatment in Patients with Normal Pre-treatment Values, All Treated Patients Protocol AI420-003

	Number (%) of Patients N = 150								
Laboratory Test	Na	Grade 1		Grade 2		Grade 3		Grade 4	
Hemoglobin	109	14	(13)	0		0		0	
WBC	138	5	(4)	1	(<1)	0		0	
Neutrophils	138	5	(4)	4	(3)	0		0	
Platelets	130	2	(2)	0		0		0	
Alkaline Phosphatase	116	7	(6)	0		0		0	
AST	123	15	(12)	1	(<1)	0		0	
ALT	119	17	(14)	1	(<1)	0		0	
Total Bilirubin	133	0		4	(3)	0		0	
BUN	134	1	(<1)	1	(<1)	0		0	
Creatinine	132	6	(5)	0		0		1	(<1)
Hypoglycemia	10	0		0		0		0	
Hyperglycemia	10	1	(10)	0		0		0	
Amylase	120	10	(8)	1	(<1)	0		0	
Hyponatremia	109	4	(4)	0		0		0	
Hypernatremia	109	4	(4)	0		0		0	
Hypokalemia	126	5	(4)	0		0		0	
Hyperkalemia	126	4	(3)	1	(<1)	0		1	(<1)
Hypochloremia	117	8	(7)	1	(<1)	1	(<1)	0	
Hyperchloremia	117	5	(4)	0		0		0	
Decreased Bicarbonate	47	2	(4)	1	(2)	0		0	
Increased Bicarbonate	47	5	(11)	2	(4)	0		0	

a For each test, number of patients with a normal pre-treatment value who had at least one during – or post-treatment value determined.
(Reference: Vol. 8, p. 86)

Worsened Laboratory Test Values During or Post-treatment in Patients with Abnormal Pre-treatment Values

There were relatively few patients who had abnormal pre-treatment laboratory values.

Three patients had abnormal pre-treatment laboratory values that worsened to Grade 3 levels during the study. Patient, 003-006, entered the study with a Grade 2 serum bicarbonate level of 36 mEq/L. The bicarbonate level increased to 38 mEq/L, (Grade 3), on Day +12. Patient, 041-004, entered into the study with a Grade 1 serum amylase level of 92 u/l without having any abdominal pain or diagnosis of pancreatitis. This level returned to normal on study Day 3; however, it was elevated to 218 mEq/L, (Grade 3), on study Day +8. A Grade 2 total bilirubin of 1.2 mg/dl was noted on entry into the study for patient, 050-002. On study Day 4, this level increased to 1.6 mg/dl, (Grade 3), and on study Day +8 the level was 1.8 mg/dl. There were no further bilirubin values obtained.

Worsened Laboratory Test Values During or Post-treatment in Patients with Abnormal Pre-treatment Values, All Treated Patients Protocol AI420-003

	Number (%) of Patients N = 150					
Laboratory Test	N[a]	Worsened to Grade 2		Worsened to Grade 3		Worsened to Grade 4
Hemoglobin	30	1	(3)	0		0
WBC	1	1	(100)	0		0
Neutrophils	0	0		0		0
Platelets	9	0		0		0
Alkaline Phosphatase	23	0		0		0
AST	14	0		0		0
ALT	19	1	(5)	0		0
Total Bilirubin	6	0		1	(17)	0
BUN	6	0		0		0
Creatinine	8	0		0		0
Hypoglycemia	5	0		0		0
Hyperglycemia	5	1	(20)	0		0
Amylase	6	0		1	(17)	0
Hyponatremia	31	1	(3)	0		0
Hypernatremia	31	0		0		0
Hypokalemia	12	1	(8)	0		0
Hyperkalemia	12	0		0		0
Hypochloremia	20	2	(10)	0		0
Hyperchloremia	20	0		0		0
Decreased Bicarbonate	26	0		0		0
Increased Bicarbonate	26	2	(8)	1	(4)	0

[a] For each test, number of patients with abnormal pre-treatment value of Grade 1, 2, or 3 who had at least one during-or post-treatment value determined.
(Reference: Vol. 8, p. 88)

Medical Officer Comment: In general the values reported in the tables above are similar to the profile seen in the gatifloxacin NDA database. Of the patients with normal liver function tests at baseline there were four who developed elevated total bilirubin levels. Two of these did not have concomitant elevation in AST/ALT and two did. The range in increased total bilirubin was 1.1-1.8 x ULN. These patients did not suffer any

adverse consequences related to these elevations. Of the remaining patients with elevated ALT/AST, none had concomitant elevations in total bilirubin. Two patients had fasting glucose values during study which were reported to be low (62-60 mg/dL). Neither patient was a diabetic. One patient had nausea and vomiting which prevented them from eating. Neither had further problems with the study medication.

8.1.4.4 OVERALL CONCLUSIONS:

APPLICANT'S CONCLUSIONS: Gatifloxacin is an effective antibiotic for the treatment of community acquired bacterial pneumonia and has an acceptable safety profile in this population.

MEDICAL OFFICER SUMMARY OF SAFETY AND EFFICACY FOR STUDY 003:

This open-label, non-randomized phase II study of gatifloxacin 400 mg PO daily, demonstrated activity in the treatment of community acquired pneumonia. The clinical response result was comparable to the other controlled studies in community acquired pneumonia. The clinical response in microbiological evaluable patients designated as cured was demonstrated for *H. influenzae* (31/33; 94%), *S. pneumoniae* (22/28, 80%), and *M. catarrhalis* (9/11; 82%). Other pathogens were reported in lower numbers. Only one case of *C. pneumoniae* was documented serologically and was considered a cure. No cases of penicillin-resistant S. pneumoniae were reported in this study.

Clinical Cure Rates

Analysis Subgroup	Cure Rate	(C.I.)
All Treated Patients	84% (126/150)	77.1%, 89.5%
Clinically Eligible	84% (113/134)	----------
Clinically Evaluable	89% (109/122)	82.5%, 94.2%

(Reference: Vol 8)

The safety profile of gatifloxacin in this study is similar to that of the larger studies reviewed in this application. Gastrointestinal symptoms including nausea and diarrhea were most frequently reported at rate similar to the other studies. No significant liver toxicity was detected in this study. No class adverse clinical events (tendon rupture, HUS, photoxoicity, seizure, cardiac dysrhythmias) were reported in this study, except for one case of seizure. This case occurred in a patient with an underlying history of seizures. Hypoglycemia occurred in 2 patients in a range of 62-60 mg/dL without clinical effect.

8.1.5 STUDY # AI420-006: An Open-Label Multicenter Non-Comparative Phase II/III Study of Oral Gatifloxacin in the Treatment of Atypical Pneumonia

8.1.5.1 STUDY DESIGN:

OBJECTIVES: 1) to establish the clinical efficacy of gatifloxacin at a dose of 400 mg QD in the treatment of atypical pneumonia; 2) to evaluate the safety profile of gatifloxacin at 400 mg QD in this patient population.

Medical Officer Comment: This study was designed chiefly to enrich the numbers of patients with documented atypical pneumonia due to M. pneumoniae, C. pneumoniae and L. pneumophila. The documentation was primarily based upon serologic testing. FDA encouraged culture diagnosis where possible.

METHODOLOGY: This was an open-label, non-comparative multicenter study.

CLINICAL PHASE: II.
STUDY PERIOD: April 12, 1997 to February 11, 1998.
INVESTIGATORS: Multiple Investigators.
STUDY CENTERS: 17 centers in the U.S. were recruited, 11 enrolled.

PROTOCOL AMENDMENDTS:
There was one amendment to the protocol, dated March 12, 1997, that specified the following changes:

- Clarification of required study procedures at each evaluation;
- Addition of procedures for sputum assessment, when produced;
- Addition of a Clinical Response category for Relapse;
- Allowance for alternate methods of serology testing;
- Clarification of use of Medication Diary;
- Correction of typographical and syntax errors.

The first (dated July 7, 1997) of two Administrative Letters allowed study drug to be taken without regard to food. The second Administrative Letter (dated September 23, 1997) provided for revised definitions of the Clinical Responses for CURED and FAILURE.

Medical Officer: FDA review of these protocol amendments was in general agreement with the applicant.

8.1.5.1.1 DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:
Male or female outpatients, 18 years or older, with a presumptive clinical diagnosis of atypical pneumonia due to *M. pneumoniae*, *L. pneumophila* and *C. pneumoniae*. The minimum criteria were: presence of a new patchy or interstitial infiltrate(s) on chest x-ray, dry, non-productive paroxysmal cough or minimally productive cough with Gram stain showing polymorphonuclear cells but no predominant organisms, and signs and symptoms of pneumonia.

Women of childbearing potential were required to have a negative pregnancy test within 2 days prior to study treatment and to agree to use effective contraceptive methods while participating in the study.

NUMBER OF PATIENTS: The planned enrollment was 200 patients. The study was terminated early because of slow accrual.

Demographics: Of the All Treated Patient group, more then half of the patients were male: the majority were white. The median age was 43 years.

Patient Disposition, All Treated Patients
Protocol AI420-006

Site Investigator	Enrolled	Treated	Number (%) of Patients Clinically Eligible	Clinically Evaluable	Microbiologically Evaluable
TOTALS	**45 (100)**	**45/45 (100)**	**41/45 (91)**	**30/45 (67)**	**7/45 (16)**
004 J. Gezon	16 (36)	16 (100)	14 (88)	6 (38)	2 (13)
015 R. Lipetz	8 (18)	8 (100)	8 (100)	6 (75)	2 (25)
001 K. Wingert	5 (11)	5 (100)	5 (100)	5 (100)	1 (20)
003 R. Ovetsky	5 (11)	5 (100)	5 (100)	5 (100)	-
002 F. Maggiacomo	3 (7)	3 (100)	3 (100)	3 (100)	2 (67)
013 G. Collins	2 (4)	2 (100)	1 (50)	1 (50)	-
018 A. Puopolo	2 (4)	2 (100)	2 (100)	2 (100)	-
005 K. Johnson	1 (2)	1 (100)	1 (100)	-	-
017 T. Hack	1 (2)	1 (100)	1 (100)	1 (100)	-
019 R. Stoltz	1 (2)	1 (100)	-	-	-
020 J. McCarty	1 (2)	1 (100)	1 (100)	1 (100)	-

(Reference: Vol. 9, p. 51)

Medical Officer Comment: One site enrolled 36% of the patients in this study; however, number of patients which are evaluable from this site are small. Overall this study contains a small number of clinically evaluable patients (30 patients), and an even smaller number of microbiologically evaluable patients (7 patients).

8.1.5.1.3 DISTRIBUTION OF PATIENTS:

Distribution of Patients in Study Populations and Reasons for Exclusion, All Treated Patients: Protocol AI420-006

Study Population/Reason Excluded	Number (%) of Patients N = 45	
Treated	45	
Clinically Eligible	41	(91)
Clinically Ineligible	4	(9)
Reason Ineligible:		
No evidence of pneumonia on pre-treatment chest x-ray	4	
Clinically Evaluable	30	(67)
Clinically Unevaluable	15	(33)
Reason Clinically Unevaluable:		
No post-treatment evaluation or chest x-ray	6	
Ineligible	4	
Inadequate dosing	4	
Other systemic antibiotic given	1	
Microbiologically Evaluable	7	(16)
Microbiologically Unevaluable	38	(84)
Reasons Unevaluable:		
No atypical pathogen identified serologically	36	
Clinically Unevaluable with positive serology	2	

(Reference: Vol. 9, p. 53)

Medical Officer Comment: Above table was verified through examination of the SAS database and CRF review. FDA is in agreement with the above. It should be noted that patients do not have sputum cultures for the most part and the information provided focuses only on the atypical pneumonia diagnosis which was based upon serology. Thus there are only 7 patients with serologic documentation of "atypical pneumonia" to review in this study. It is of interest to note the clinical response of the "microbiologically" diagnosed pneumonias, but since there is no additional culture data reported, the numbers are small, and this being an open-label, non-randomized study these data can only be considered supportive.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: 400 mg gatifloxacin film-coated tablets (Lot No. N97004) taken orally (PO) once a day (QD).

8.5.1.4 DURATION OF TREATMENT: Patients were treated for 14 days. Study medication was recorded for 44/45 (98%) patients. Study medication dosing could not be determined for one patient (004-012) who was lost to follow-up.

Overall, the median duration of dosing was 14 days and 34 (77%) patients received 13 or 14 days (the full course). Nine additional patients received 7 days or less of study medication. Four of the five patients who received between 5 and 7 days withdrew due to an adverse event or abnormal laboratory; the fifth patient (003-002) was considered a clinical failure after 7 days of study therapy.

Four patients (9%) received one dose of study medication. Three of the four patients who received 1 dose of gatifloxacin withdrew due to adverse events. The fourth patient (019-001) who received 1 dose was discontinued after the investigator deemed the patient ineligible because of a normal pre-treatment chest x-ray by radiologist interpretation.

8.1.5.1.5 CRITERIA FOR EVALUATION:
A medical history, complete physical examination, vital signs, clinical evaluation of the signs and symptoms, and chest x-ray, and various specimens, including acute phase serology were obtained within 48 hours prior to the start of gatifloxacin treatment.

Evaluation of the patient's clinical and safety status was made between Days 3 and 5 of study drug therapy. Between 1 and 3 days after the end of treatment, a follow-up telephone contact was made; if the patient's signs and symptoms had not resolved at this time, an immediate office visit was scheduled in which the post-treatment procedures were performed. For all other patients, the post-treatment visit (i.e., Test of Cure Visit) was scheduled between Days 7 and 14 after the end of study drug therapy in which the patient was evaluated as thoroughly as was done at the pre-treatment visit. In addition, there was an extended follow-up visit between Days 21 and 28 to collect a convalescent serology specimen and evaluate the occurrence of relapse, new infections and adverse events.

Clinical response was determined at the Test of Cure Visit between Day +5 to Day +28. Treatment failures could be assessed at any time during the treatment and follow-up periods but these patients had to receive a minimum of three days of therapy.

8.1.5.1.6 OUTCOME ANALYSIS

Efficacy Analyses: A clinical response of cured included all patients whose signs and symptoms of pneumonia had resolved or improved without the need for further antimicrobial therapy and chest x-ray abnormalities had either improved or not progressed. A clinical response of failure indicated no clinical or radiographic response of the original infection to treatment with study drug.

Safety Analyses: Data included for safety evaluation were: clinical signs and symptoms, physical examinations, vital sign measurements, clinical laboratory tests, and adverse events.

8.1.5.1.7 STATISTICAL METHODS: There were four study populations of interest:
All Treated Patients: All patients known to have received at least one dose of gatifloxacin.
Clinically Eligible Patients: All Treated Patients with a diagnosis of pneumonia presumably due to atypical pathogens at entry.
Clinically Evaluable Patients: All Eligible Patients who had: a duration of dosing of at least 5 days (with the exception of at least 3 days for early treatment failures) and received at least 80% of the expected number of doses; a post-treatment clinical assessment within the Day +5 to Day +28 window or end of treatment assessment if the subject was an early discontinuation due to treatment failure; a chest x-ray performed during or at the Test of Cure Visit; and did not receive any presumably effective systemic antibacterials between the time of the pre-treatment visit and the post-treatment assessment.
Microbiologically Evaluable Patients: All Clinically Evaluable Patients having an atypical pathogen documented by serological testing.

Medical Officer Comment: Because of the similarity in analysis and evaluation of this study to the previously described comparative trials, this reviewer will not repeat comments already made in the previous reviews.

8.1.5.2 EFFICACY RESULTS:
8.1.5.2.1 Clinical Efficacy: Clinical Response - Ninety percent (27/30) of the clinically evaluable patients had a clinical response of cured(95% CI, 73.5%, 97.9%).. The clinical cure rate was not affected by any prognostic factor such as patient age, history of comorbid disease, recent history of pneumonia and chest x-ray interpretation or the severity of pneumonia.

Clinical Response, Clinically Evaluable Patients
Protocol AI420-006

	Number (%) of Patients		
Clinical Response	N = 30		95% Confidence Interval
Cured	27	(90)	73.5%, 97.9%
Failure	3	(10)	

(Reference: Vol. 9, p. 70)

None of the clinically evaluable patients relapsed.

Treatment Failures, Clinically Evaluable Patients
Protocol AI420-006

Patient Number	Pre-treatment Organism	Treatment Duration (days)	Time of Failure (Study Day)	Reason Clinical Response is Failure, New, Worse, Unchanged Primary Signs/Symptoms	Post-treatment Chest X-ray
003-002	No	7	L7	worsening cough	improved
013-002	No	14	+9	unchanged cough	improved
018-002	No	14	+12	worsening cough	normal

(Reference: Vol.9, p. 71)

Of the 41 clinically eligible patients, 28 (68%) were cured and 4 patients failed . One of the clinical failures (patient 004-003) was in a patient who tested positive for *M. pneumoniae*. That patient had persistent x-ray abnormalities 35 days after the end of therapy.

Clinical Cure Rates

Analysis Group	Cure Rate	(C.I.)
All Treated Patients	62% (28/45)	46.5%, 76.2%
Eligible Patients	68% (28/41)	----------
Evaluable Patients	90% (27/30)	73.5%, 97.9%

(Reference: Vol 9)

Medical Officer Comment: FDA review of SAS data sets and CRFs is in agreement with the applicant's analysis of efficacy. The clinical cure rate in the evaluable patient subset is similar to that seen in the control trials. The lower cure rate in clinically eligible patients was due to the inadequate treatment and lost to follow up at one site (004). The other sites had similar rates of cure when eligible and evaluable patients were considered by site.

8.1.5.2.2. MICROBIOLOGICAL EFFICACY:

Medical Officer Comment: As noted above, this study concerned itself with reporting only the atypical pathogens. Thus, the microbiologic efficacy results reflect only the clinical outcomes of patients with serologic diagnosis at baseline.

Pre-treatment Pathogens Identified by Serological Testing, All Treated Patients Protocol AI420-006

	Number (%) of Patients N = 45	
Patients with No Pathogen	36	(80)
Patients with an Atypical Pathogen	9	(20)
Pathogen		
M. pneumoniae	5	(11)
C. pneumoniae	2	(4)
L. pneumophila	2	(4)

(Reference: Vol. 9, p. 60)

In seven patients, the diagnosis was based on a simple high titer in either the pre-treatment serum, the post-treatment serum or both. In two patients, a four fold rise in IgG for *M. pneumoniae* between pre-treatment and convalescent sera was noted.

Medical Officer Comment: Note that two of these patients were clinically unevaluable #4-00003, #15-00001). The first had not Test of Cure visit but later CXR showed progression of radiographic abnormalities, and the second patient was lost to follow up.

Serological Results for Atypical Pathogens[a,b]
Protocol AI420-006

	M. pneumoniae Acute/Convalescent		*C. pneumoniae* Acute/Convalescent	*L. pneumophila* Serogroups 1-6 Acute/Convalescent	Clinically Evaluable
Patient	IgG	IgM	IgG	IgG/IgM/IgA	Yes/No
001-002	32/>256	<16/<16	<64/<64	<256/<256	Yes
002-002	64/64	<16/<16	<64/<64	<256/<256	Yes
002-003	<32/<32	<16/<16	>1024/>1024	<256/<256	Yes
004-003	32/64	<16/16	64/128	<256/<256	No
004-006	<32/<32	<16/<16	--/64	256/256	Yes
004-014	<32/64	<16/<16	<64/<64	<256/<256	Yes
015-001	256/256	<16/<16	<64/<64	<256/<256	No
015-003	<32/<32	<16/<16	>1024/>1024	<256/<256	Yes
015-008	<32/<32	<16/<16	<64/<64	256/256	Yes

a Results are presented as the titer reciprocal.
b *C. pneumoniae* IgM were all <1:10.

Medical Officer Note: It should be noted that all of the patients diagnosed with atypical pathogens were diagnosed by serology. The majority having a single high titer, which at best is presumptive. These patients will be added to the summary of documented pathogens from the CAP studies in the overall summary of pathogens. The numbers reported here are too small for independent conclusion on the overall efficacy of gatifloxacin for the treatment of atypical pneumonia caused by L. pneumonphila, M. pneumoniae, C. pneumoniae.

Overall, for the documented atypical pathogens the clinical cure rate was high and comparable to the other comparative clinical trials.

8.1.5.3 SAFETY RESULTS:

8.1.5.3.1 Overall and Related Adverse Clinical Events:

Gatifloxacin was well tolerated. The most common adverse clinical events were related to signs and symptoms of pneumonia, in particular *L. pneumophila, C. pneumoniae, M. pneumoniae*, abnormal breath sounds (20% of patients), pharyngitis (16%), dyspnea, rhinitis, increased sputum, chest pain and coughing, each occurring at a frequency of 11%. No female patient developed vaginitis.

Adverse Clinical Events of All Causes, All Treated Patients Protocol AI420-006

	Number (%) of Patients N = 45							
Adverse Clinical Event[a,b]	Drug Related		Not Drug Related		Unassessed		Total	
Any Adverse Clinical Event	16	(36)	18	(40)	1	(2)	35	(78)
Abnormal Breath Sounds	-		9	(20)	-		9	(20)
Pharyngitis	-		7	(16)	-		7	(16)
Dyspnea	1	(2)	4	(9)	-		5	(11)
Vomiting	3	(7)	2	(4)	-		5	(11)
Rhinitis	1	(2)	4	(9)	-		5	(11)
Increased Sputum	-		5	(11)	-		5	(11)
Chest Pain	2	(4)	3	(7)	-		5	(11)
Coughing	-		5	(11)	-		5	(11)
Nausea	2	(4)	2	(4)	-		4	(9)
Insomnia	2	(4)	1	(2)	-		3	(7)
Nervousness	2	(4)	1	(2)	-		3	(7)
Diarrhea	2	(4)	1	(2)	-		3	(7)
Malaise	-		3	(7)	-		3	(7)
Pain	-		2	(4)	1	(2)	3	(7)
Headache	-		3	(7)	-		3	(7)
Myalgia	-		3	(7)	-		3	(7)
Rash	2	(4)	-		-		2	(4)
Sinusitis	-		2	(4)	-		2	(4)
Paraesthesia	1	(2)	-		1	(2)	2	(4)
Dizziness	1	(2)	1	(2)	-		2	(4)
Dyspepsia	1	(2)	1	(2)	-		2	(4)

a All adverse events occurring in ≥3% of the total number of treated patients.
b Patients may have more than one adverse clinical event.
(Reference: Vol. 9, p. 79)

Related Adverse Clinical Events:
Sixteen (36%) patients experienced adverse clinical events that were considered related to gatifloxacin treatment. Most of the 36% of drug related adverse events were mild (9%

of patients) to moderate (18%) in severity. The most common were vomiting (7% of patients) and nausea, rash, insomnia, nervousness, chest pain and diarrhea, each occurring at a frequency of 4%.

One patient (004-001) experienced a very severe adverse event, which consisted of an allergic reaction with very severe dyspnea, severe cyanosis, hyperventilation and rash within 60 minutes of taking the first dose.

Multiple adverse events considered related to study medication by the investigator were reported for three patients: (004-001), (003-004) and (004-005). Patient (004-001) experienced a serious allergic reaction. Patient (003-004), who had a pulmonary history of COPD, experienced several adverse events that were attributed to study medication by the investigator. These included chest pain, rhinitis, bladder spasm, all occurring post-treatment. On Day 6, this patient was discontinued from study medication due to a swollen lip and on Day +3 developed colitis caused by *C. difficile* for which she received antimicrobials. Patient (004-005) experienced three adverse events believed related to study medication by the investigator: moderate insomnia, moderate nervousness and mild dizziness, all with onset during treatment. On Day 6, this patient was discontinued from study medication due to insomnia and nervousness and on Day +1 was prescribed clarithromycin for continued treatment of pneumonia.

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Drug Related Adverse Clinical Events, All Treated Patients
Protocol AI420-006

	Number (%) of Patients N = 45									
Adverse Clinical Event[a]	Mild		Moderate		Severe		Very Severe		Total	
Any Related Adverse Clinical Event	4	(9)	8	(18)	3	(7)	1	(2)	16	(36)
Vomiting	2	(4)	1	(2)	-		-		3	(7)
Nausea	-		1	(2)	1	(2)	-		2	(4)
Rash	-		1	(2)	1	(2)	-		2	(4)
Insomnia	-		1	(2)	1	(2)	-		2	(4)
Nervousness	-		1	(2)	1	(2)	-		2	(4)
Chest Pain	2	(4)	-		-		-		2	(4)
Diarrhea	-		2	(4)	-		-		2	(4)
Paraesthesia	1	(2)	-		-		-		1	(2)
Rhinitis	1	(2)	-		-		-		1	(2)
Allergic Reaction	-		-		-		1	(2)	1	(2)
Spasm (bladder)	1	(2)	-		-		-		1	(2)
Dyspnea	-		-		-		1	(2)	1	(2)
Dyspepsia	-		1	(2)	-		-		1	(2)
Edema	1	(2)	-		-		-		1	(2)
Hematemesis	-		1	(2)	-		-		1	(2)
Hyperventilation	-		-		1	(2)	-		1	(2)
Dizziness	1	(2)	-		-		-		1	(2)
Mouth Ulcer	-		1	(2)	-		-		1	(2)
Sweating	1	(2)	-		-		-		1	(2)
Colitis	-		-		1	(2)	-		1	(2)
Cyanosis	-		-		1	(2)	-		1	(2)
Dry Mouth	1	(2)	-		-		-		1	(2)

[a] Patients may have more than one drug-related adverse clinical events.
(Reference Vol. 9, p. 81)

Medical Officer Comment: The types of adverse events reported above are similar to those reported in the larger comparative CAP studies.

No evidence of cardiac abnormalities were documented in this study. No tendon rupture, pancreatitis, phototoxicity or seizures were reported in this study.

8.1.5.3.2 Discontinuation Due to Adverse Clinical Events:

Seven patients discontinued the study due to adverse clinical events, one each for: edema of the lip, allergic reaction, mouth ulcer, insomnia and shakiness, hematemesis, vomiting and nausea, hypoxia and pneumonia. Six of the seven discontinuations, the exception being hypoxia and pneumonia, were attributed to study medication by the investigator and three occurred after taking only one dose. In addition, one patient discontinued therapy prematurely due to a laboratory test abnormality (elevated liver function test results) that was noted after five doses had been received (see laboratory abnormalities for further discussion of patient). It is noteworthy that seven of the eight patients were enrolled at the same site. Seven of the eight discontinuations were attributed to study medication and three occurred after taking one dose.

Discontinuation of Study Medication Due to Adverse Clinical Events or Laboratory Abnormality, All Treated Patients
Protocol AI420-006

Patient Number	Adverse Clinical Event	Relationship to Gatifloxacin	Duration of Dosing (Days)	Onset of Adverse Clinical Event (Study Day)
003-004	Edema of lip	possible	6	6
004-001	Allergic reaction	certain	1	1
004-004	Mouth ulcer	certain	12	11
004-005	Insomnia, Shakiness	probable	6	1
004-010	Hematemesis	probable	7	6
004-011	Vomiting, Nausea	certain	1	1
004-013	Hypoxia, Pneumonia	unrelated	1	1
004-008	Abnormal lab, Elevated LFTs	certain	5	4

Medical Officer Comment: Note that the first patient described was admitted to the hospital and treated for an allergic reaction that consisted of throat tightening and difficulty breathing. This patient was released the next day in good condition. The digestive system adverse events were mainly nausea. Three patients were noted to have "elevated LFTs". One of these had significant elevation and is described in the laboratory abnormalities section. This patient resolved with no apparent residual effects. One of these patients was diagnosed with infectious mononucleosis where the liver abnormalities were felt by the clinician not to be related to study drug.

8.1.5.3.3 Serious Adverse Clinical Events:

Four patients (9%) experienced serious adverse clinical events. One serious adverse event was considered drug related in one patient previously described. The other three serious adverse events were not considered drug related. They consisted of a delirium tremens

due to alcohol withdrawal and worsening of pulmonary symptoms. Following are summaries of the patients who reported serious adverse events.

- Patient 003-003 was hospitalized with acute exacerbation of COPD on Day 3. She completed 14 days of gatifloxacin and was considered a clinical cure.
- Patient 004-001 experienced a severe allergic reaction after one dose of gatifloxacin and was discontinued from the study. This patient is discussed in Appendix 14.
- Patient 004-007 was hospitalized with worsening pneumonia on Day 2. He completed 14 days of gatifloxacin and was considered a clinical cure.
- Patient 004-013 was hospitalized with hypoxia and worsening pneumonia on Day 1. While hospitalized, he experienced delirium tremens that the investigator attributed to alcohol withdrawal. He was discontinued from the study after receiving one dose and assessed unable to determine for a clinical response.

Serious Adverse Clinical Events of All Causes,
All Treated Patients
Protocol AI420-006

	Number (%) of Patients N = 45							
Serious Adverse Clinical Event[a]	Related		Not Related		Unknown/ Unassessed	Total		
Any Serious Adverse Clinical Event	1	(2)	3	(7)	-	4	(9)	
Allergic Reaction	1	(2)	-		-	1	(2)	
Delirium Tremens	-		1	(2)	-	1	(2)	
Lung Disorder (COPD Exacerbation)	-		1	(2)	-	1	(2)	
Hypoxia	-		1	(2)	-	1	(2)	
Pneumonia	-		2	(4)	-	2	(4)	

[a] A patient may have more than one serious adverse clinical event.
(Reference: Vol. 9, p. 83)

Deaths: There were no deaths in this study.

Medical Officer Comment: FDA's review of the applicant's adverse event data is in agreement with the above analysis. Allergic reactions can be seen with antibiotics in a small number of patients. This will be addressed in the labeling.

8.1.5.3.5 Laboratory Abnormalities:

Very few patients with normal pre-treatment laboratory values developed abnormalities during or post-treatment. Most abnormalities that did occur were mild (Grade 1) with elevated AST and ALT, and decreased hemoglobin, leukocytes and neutropenia being most common. In patients with abnormal (Grade 1, 2 or 3) pre-treatment values, worsening to a higher grade during or post-treatment was infrequent. Three patients experienced worsening to Grade 3.

Patients with Normal Pre-treatment Laboratory Values
Very few patients with normal baseline values developed laboratory abnormalities during or post-treatment Most abnormalities that did occur were mild (Grade 1). The most common abnormalities were elevated AST and ALT and decreased hemoglobin, leukocytes and neutropenia.

Two patients experienced neutropenia. On Day 1, Patient (001-004) had a neutrophil count of 7.7 cells x 1000/μL that decreased to 0.8 cells x 1000/μL on Day 5 and returned to normal range by Day +8. Patient (018-001) had a normal pre-treatment neutrophil count that decreased to 1.0 cells x 1000/μL with no clinical significance and returned to normal range by Day +13. At pre-treatment, patient (001-005) had a normal total bilirubin (1 mg/dL) that increased to grade 2 (1.1 mg/dL) on Day +7 with no clinical significance. At pre-treatment, patient (004-008) had normal ALT that increased more than 10 fold to Grade 3 (416 U/L) by Day 4 and resulted in discontinuation on Day 5. This patient also had an abnormal Grade 1 AST (66 U/L) at pre-treatment. There was no recorded clinical significance associated with the elevated ALT that returned to normal range by Day +28. This was a 73 year old white female.

Abnormal Laboratory Test Values During or Post-treatment in Patients with Normal Pre-treatment Values, All Treated Patients Protocol AI420-006

Laboratory Test	Number (%) of Patients								
	N[a]	Grade 1		Grade 2		Grade 3		Grade 4	
Hemoglobin	31	6	(19)	-		-		-	
WBC	33	4	(12)	-		-		-	
Neutrophils	33	2	(6)	1	(3)	1	(3)	-	
Platelets	32	-		-		-		-	
Alkaline Phosphatase	31	1	(3)	1	(3)	-		-	
AST/SGOT	33	4	(12)	-		-		-	
ALT/SGPT	29	3	(10)	-		1	(3)	-	
Total Bilirubin	34	-		1	(3)	-		-	
BUN	39	1	(3)	-		-		-	
Creatinine	39	1	(3)	-		-		-	
Amylase	32	2	(6)	-		-		-	
Hyponatremia	33	2	(6)	-		-		-	
Hypernatremia	33	-		-		-		-	
Hypokalemia	35	-		-		-		-	
Hyperkalemia	35	-		-		-		-	
Hypochloremia	35	-		-		-		-	
Hyperchloremia	35	-		-		-		-	
Decreased Bicarbonate	30	1	(3)	-		-		-	
Increased Bicarbonate	30	-		-		-		-	

[a] For each test, number of patients with a normal pre-treatment value who had at least one during- or post-treatment value determined.
(Reference: Vol. 9, p. 86)

Medical Officer Comment: Of the two patients with changes in amylase, neither had clinical symptoms of pancreatitis. Review of the LFTs reveals no serious outcomes even in the grade 3 patient described above. Of patients with normal baseline liver function tests, none had an elevation of total bilirubin, and only one each had a rise in AST or ALT (1.2 X ULN). These changes were not clinically significant.

Patients with Abnormal Pre-treatment Laboratory Values

Few patients experienced worsening of abnormal pre-treatment laboratory values. At pre-treatment, patient (004-008) had grade 1 AST (66 U/L) that worsened to grade 3 (308 U/L) by Day 4, decreased to grade 2 (192 U/L) at the time of discontinuation on Day 5 and returned to normal by Day +28. This patient also had elevated ALT that was normal at pre-treatment and elevated to grade 3 (416 U/L) by Day 4. At enrollment, patient (013-001) had grade 2 AST (147 U/L) that worsened to grade 3 (298 U/L) by Day 6 and returned to grade 2 (123 U/L) by Day +8. This patient completed 14 days of study medication. The investigator attributed the elevated LFTs to infectious mononucleosis that was confirmed by laboratory test on Day 8.

Worsened Laboratory Test Values During or Post-treatment in Patients with AbnormalPre-treatment Values, All Treated Patients
Protocol AI420-006

		Number (%) of Patients		
Laboratory Test	N[a]	Worsened to Grade 2	Worsened to Grade 3	Worsened to Grade 4
Hemoglobin	3	-	-	-
WBC	1	-	-	-
Neutrophils	1	-	-	-
Platelets	2	-	-	-
Alkaline Phosphatase	8	1 (13)	-	-
AST/SGOT	6	-	2 (33)	-
ALT/SGPT	10	-	-	-
Total Bilirubin	5	-	-	-
BUN	-	-	-	-
Creatinine	-	-	-	-
Amylase	-	-	-	-
Hyponatremia	6	1 (17)	-	-
Hypernatremia	6	-	-	-
Hypokalemia	4	-	-	-
Hyperkalemia	4	-	-	-
Hypochloremia	4	-	1 (25)	-
Hyperchloremia	4	-	-	-
Decreased Bicarbonate	9	-	-	-
Increased Bicarbonate	9	1 (11)	-	-

a For each test, number of patients with an abnormal pre-treatment value who had at least one during or post-treatment value determined. (Reference: Vol. 9, p. 88)

Medical Officer Comment: FDA is in agreement with the applicant's analysis. For the most part these abnormalities were not clinically significant. The profile is similar to that seen in the larger CAP studies.

8.1.5.4 OVERALL CONCLUSIONS:

APPLICANT'S CONCLUSIONS: This study provides preliminary evidence of activity of gatifloxacin in patients with pneumonia including those with atypical pathogens.

MEDICAL OFFICER SUMMARY OF SAFETY AND EFFICACY FOR STUDY 006

This open-label, non-randomized phase II study of gatifloxacin 500 mg PO daily, demonstrated activity in the treatment of community acquired pneumonia. This study was primarily conducted to study the cases documented to be due to pathogens responsible for causing "atypical pneumonia"; i.e. *M. pneumoniae, C. pneumoniae, L. pneumophila.* As such it was fairly weak in its results. Of the 45 patients treated in this study, 30 were clinically evaluable and only 7 were microbiologically evaluable. The cure rate for the 30 evaluable patients was 90% (27/30). Of the microbiologically evaluable patients, all were diagnosed by serologic methodology (5 = *M. pneumoniae*, 2 = *C. pneumoniae*, 2 = *L. pneumophila* [2 patients had multiple positive serology]). PCR was not done in these patients, and *L. pneumophila* urinary antigen was not performed. It is questionable as to whether either of these cases can be considered 'confirmed infections" due to *L. pneumophila.* All of the microbiologically evaluable patients were considered clinical cures. This study does not add much additional information to the controlled trials regarding the activity of gatifloxacin for these atypical pathogens because of the small numbers attained in this study.

Clinical Cure Rates

Analysis Group	Cure Rate	(C.I.)
All Treated Patients	62% (28/45)	46.5%, 76.2%
Eligible Patients	68% (28/41)	----------
Evaluable Patients	90% (27/30)	73.5%, 97.9%

(Reference: Vol 9)

Clinical Cure rates were somewhat low in the all treated patient group, primarily because of the loss to follow-up. The Evaluable Patient analysis is similar to that of the other larger studies.

The safety profile of gatifloxacin in this study is similar to that of the larger studies reviewed in this application. Gastrointestinal symptoms including nausea and diarrhea were most frequently reported, although at a rate comparable to the other studies (4% drug related). No significant liver toxicity was detected in this study. No drug class

related adverse clinical events were reported in this study (tendon rupture, seizure, HUS, phototoxicity, cardiac dysrhythmias, hypoglycemia).

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APPENDIX A

Atypical Pathogen Serologic Data

* indicates culture positive cases of *M. pneumoniae*

Where serologic results are unchanged from the pre- value, only one value is listed.
Where a pre- or post- test was not performed it is listed as ND.

STUDY 006

Mycoplasma pneumoniae STUDY 006

PID	Additional Pathogens Isolated	Clinical Response	PCR	IgG/ (pre/post)	IgM (pre/post)	DRUG
00001 00002		Cured	nd	32/<256	<16/nd	A
00002 00902		Cured	nd	64	46/<16	A
00004 00014	S. pyogenes	Cured	nd	<32/64	<16/nd	A

Chlamydia Pneumoniae STUDY 006

PID	Additional Pathogens Isolated	Clinical Response	PCR	IgG/ (pre/post)	IgM (pre/post)	DRUG
00002 00003		Cured	nd	>1024/nd	<10/nd	A
00015 00003		Cured	nd	>1024/nd	<10/nd	A

Legionella pneumophila STUDY 006

PID	Additional Pathogens Isolated	Clinical Response	PCR	Urinary Antigen	Combined Titer	DRUG
00004 00006		Cured			256/nd	A
00015 00008		Cured			256	A

GATIFLOXACIN = DRUG A

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Signature Sheet:

/S/

Joyce Korvick, M.D., M.P.H.
Reviewing Medical Officer, DSPIDP

Concurrences:

/S/

Joyce Korvick, M.D., M.P.H.
Lead Medical Reviewer
Division of Special Pathogen and Immunologic Drug Products

/S/ 11/22/99

Marc Cavaillé-Coll, M.D., Ph. D.
Medical Team Leader
Division of Special Pathogen and Immunologic Drug Products

/S/

Mark Goldberger, M.D., M.P.H.
Division Director
Division of Special Pathogen and Immunologic Drug Products

cc:
Original NDA 21-061
HFD-590/Div. Dir/Goldberger
HFD-590/Dep. Div. Dir/Albrecht
HFD-590/TI/Cavaillé-Coll
HFD-590/MO/Korvick
HFD-590/MO/Roca
HFD-590/Chem/Smith
HFD-520/Micro/Altaie
HFD-880/BioPharm/Uhl
HFD-520/Pharmtox/Ellis
HFD-725/Biometrics/Silliman
HFD-590/RPM/Atkins

8.2 Medical Officer Review of NDA 21-061: Gatifloxacin (Tequin™) for the treatment of Acute Exacerbations of Chronic Bronchitis

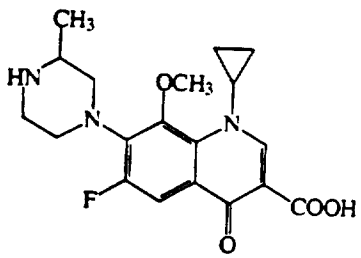
Date Submitted: 28 December 1998
Date Received : 29 December 1998
Date Assigned: 16 March 1999
Date Completed: 1 November 1999

Reviewer: Ziad Akl, M.D.

Applicant: Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, Connecticut 06492
203-677-6883
Contact person: Douglas Kriesel, Ph.D.

Drug:

Proprietary name - Tequin ™
Generic name - Gatifloxacin
Chemical name - (±)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolone carboxylic acid sesquihydrate
Molecular formula - $C_{19}H_{22}FN_3O_4 \cdot 1.5\ H_2O$
Molecular weight - 402.42 (sesquihydrate)
Molecular structure -



• 1.5 H_2O

Drug Class: 8-methoxyfluoroquinolone antibacterial

Formulation: (capsule, suspension, lyophilized powder, etc.)

Route of administration: Oral; 200 mg and 400 mg tablets

Related NDA: 21-062

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Medical Review Summary

I. Introduction

The repertoire of antibiotics available for the treatment of acute exacerbations of chronic bronchitis (AECB) includes the penicillins, cephalosporins, newer macrolides and fluoroquinolones. However, therapeutic options for AECB have been narrowed as the major pathogens associated with these exacerbations continue to develop antibiotic resistance that made the discovery and development of new antibiotics for the treatment of AECB clearly warranted.
Gatifloxacin has a broad spectrum of activity in vitro, encompassing all of the respiratory pathogens associated with AECB, both Gram-positive (*S. pneumoniae*, including penicillin-resistant strains) and Gram-negative (*H. influenzae, H. parainfluenzae and M. catarrhalis*). It also has activity against *Mycoplasma pneumoniae, Legionella and Chlamydia pneumoniae.*

Other fluoroquinolones indicated for AECB include:

- Ciprofloxacin, 500 to 750 mg PO q12h for 7 to 14 days, for *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis* and *Streptococcus pneumoniae.*
- Ofloxacin, 400 mg PO or IV q12h for 10 days, for *Haemophilus influenzae* and *Streptococcus pneumoniae.*
- Levofloxacin, 500 mg PO or IV q24h for 7 days, for *Staphylococcus aureus, Haemophilus parainfluenzae,* and *Moraxella catarrhalis.*
- Lomefloxacin, 400 mg PO QD for 10 days, for *Haemophilus influenzae* and *Moraxella catarrhalis.*
- Grepafloxacin, 400 or 600 mg PO QD for 10 days, for *Haemophilus influenzae, Streptococcus pneumoniae,* and *Moraxella catarrhalis.*
- Sparfloxacin, 200 mg PO on the first day, then 200 mg QD for a total of 10 days, for *Chlamydia pneumoniae, Enterobacter cloacae, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Staphylococcus aureus* , and *Streptococcus pneumoniae.*

II. Proposed Indication

The applicant is requesting approval of the following wording for the AECB indication:
Acute bacterial exacerbation of chronic bronchitis caused by *Streptococcus pneumoniae (penicillin-susceptible and penicillin-resistant strains), Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Klebsiella pneumoniae, Enterobacter cloacae or Staphylococcus aureus.*

Under "**DOSAGE AND ADMINISTRATION**", the proposed regimen for the treatment of AECB is 400 mg of gatifloxacin once daily for 7 to 10 days.

III. Studies Submitted

The objective of the applicant is to demonstrate clinical efficacy and safety of gatifloxacin 400 mg PO QD for 7 to 10 days in AECB by demonstrating equivalence to other drugs approved for the indication. Three studies, generally similar in design, were submitted to FDA for review.

Table 1 Overview of Studies

Protocol/Phase	Study Type	Dose/Duration	Number of Patients
AI420-004 (study 4) Phase II	Multicenter, open-label non-comparative trial	Gatifloxacin 400 mg PO qd for 10 days	210 enrolled, 162 evaluable
AI420-001 (study 1) Phase III	Multicenter, randomized, double-blind controlled trial	Gatifloxacin 400 mg PO qd vs. Levofloxacin 500 mg PO qd for 7-10 days	360 enrolled, 296 evaluable
AI420-020 (study 20) Phase III	Multicenter, randomized, double-blind controlled trial	Gatifloxacin 400 mg PO qd vs. cefuroxime axetil 250 mg PO BID for 7-10 days	340 enrolled, 284 evaluable

Studies 1 and 4 were conducted at U.S. study sites, but study 20 enrolled patients from the U.S., Argentina, Brazil, Mexico, Puerto Rico, South Africa and Canada. Protocol inclusion criteria required adult patients to have a clinical diagnosis of AECB defined as the presence of purulent sputum confirmed by Gram stain examination (>25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low power field) and the presence of at least two of the following signs and symptoms: increased cough and/or dyspnea; increased sputum volume; and increased sputum purulence. Patients with evidence of pneumonia on chest x-ray were excluded, as were patients with immune deficiency, renal or hepatic dysfunction or malabsorption syndromes. The criterion of <10 epithelial cells/LPF was later relaxed by the applicant via the analysis plan of studies 1 and 20 to include patients who were shown at the central laboratory reading of the sputum Gram stain to have >10 epithelial cells/LPF. The applicant's explanation was that "epithelial cells, when associated with >25 PMNs, only indicate that the purulent bronchial secretions have been contaminated by mouth flora. It does not detract from the clinical findings and confirms that the patient has purulent sputum". The applicant also cited a precedent where disregard of this criterion was acceptable to FDA, and provided FDA with a list of those patients who were enrolled despite having >10 epithelial cells/LPF. Patient assessments as outlined in the protocols were performed at baseline (within 48 hours before dosing), during the study (Day 3 to 5 of therapy), near the end of therapy (Day +1 to +3), post-therapy (Day +7 to +14; this is referred to as test of cure visit or TOC) and at a final follow-up (Day +21 to +28). In the final efficacy analyses, the TOC time window was +5 to +18 days following completion of therapy to allow for scheduling conflicts. Clinical response was based on signs and symptoms and bacteriologic response was based on culture results or, if there was no source to culture, the clinical assessment at the TOC visit. Relapse was evaluated at the extended follow-up assessment.

For studies 1 and 20, each patient was assigned a clinical response of Cured, Failure, or Unable to Determine (UTD). For study 4, there was an additional "improved" category. Each pre-treatment pathogen was assigned a bacteriologic response of Eradicated, Presumed Eradicated, Persisted, Presumed Persisted or Unable to Determine. There were four study populations of interest: All Treated Patients, Eligible Patients (All Treated Patients with a diagnosis of AECB and no evidence of pneumonia), Clinically Evaluable Patients (All Eligible Patients who had a duration of dosing of at least 5 days or at least 3 days for treatment failures, had a post-treatment clinical assessment, and did not receive other systemic antibacterial agents), and Microbiologically Evaluable Patients (All Clinically Evaluable Patients who had at least one pathogen isolated pre-treatment non-resistant to the study drugs).

IV. Results

Clinical Response

Clinical response is shown in tables 3 through 6. To examine the robustness of the applicant's analysis results, the following analyses were performed by the reviewer:

- The applicant's definition of cure in studies 1 and 20 included those patients whose symptoms improved as well as those whose symptoms returned to baseline. Therefore a separate analysis was done that considered as cured only those patients whose 3 cardinal symptoms of cough, dyspnea and sputum production either returned to baseline at the TOC visit, or were only improved at the TOC visit but returned to baseline at the extended follow-up visit. This is referred to below as "reviewer's analysis #1".

- The applicant included in the analysis those patients who had >10 epithelial cells/LPF in their sputum. Another separate analysis was done that considered ineligible those patients whose sputum contained >10 epithelial cells/LPF. This was referred to as "reviewer's analysis #2".

- A third analysis was done that took into account both above issues. This was referred to as "reviewer's analysis #3".

Table 3 Clinical Efficacy of Gatifloxacin and Comparator (Applicant' Analysis)

Study	Drug	Clinically Evaluable Patients Efficacy Rate	95% C.I.*	Eligible Patients Efficacy Rate	95% C.I.*
Study 4	Gatifloxacin	88% (143/162)	(82%, 93%)	80% (143/178)	(74%, 86%)
Study 1	Gatifloxacin	88% (127/145)	(-14.6%, 6.2%)	77% (129/167)	(-17.6%, 4.5%)
	Levofloxacin	92% (139/151)		83% (141/169)	
Study 20	Gatifloxacin	86% (124/145)	(-4.8%, 11.4%)	81% (126/156)	(-6.9%, 10.6%)
	Cefuroxime	83% (115/139)		79% (121/153)	

* 95% Confidence Interval for the cure rate for study 4, and around the difference in cure rates for studies 1 and 20.

Table 4 Clinical Efficacy of Gatifloxacin and Comparator (Reviewer's Analysis #1)

Study	Drug	Clinically Evaluable Patients Efficacy Rate	95% C.I.	Eligible Patients Efficacy Rate	95% C.I.*
Study 1	Gatifloxacin	70% (102/145)	(-13.8%, 5.6%)	62% (103/167)	(-15.9%, 4.3%)
	Levofloxacin	75% (113/151)		68% (114/169)	
Study 20	Gatifloxacin	61% (88/145)	(-19.24%, 23.28%)	58% (90/156)	(-18.89%, 19.54%)
	Cefuroxime	59% (82/139)		58% (88/153)	

*95% Confidence Interval around the difference in cure rates.

Table 5 Clinical Efficacy of Gatifloxacin and Comparator (Reviewer's Analysis #2)

Study	Drug	Clinically Evaluable Patients Efficacy Rate	95% C.I.	Eligible Patients Efficacy Rate	95% C.I.*
Study 1	Gatifloxacin	87% (115/132)	(-16.3%, 9.1%)	77% (117/152)	(-19.8%, 8.8%)
	Levofloxacin	91% (120/132)		82% (122/149)	
Study 20	Gatifloxacin	85% (112/132)	(-5.61%, 11.75%)	81% (114/140)	(-5.54%, 12.87%)
	Cefuroxime	82% (104/127)		78% (109/140)	

*95% Confidence Interval around the difference in cure rates.

Table 6 Clinical Efficacy of Gatifloxacin and Comparator (Reviewer's Analysis #3)

Study	Drug	Clinically Evaluable Patients Efficacy Rate	95% C.I.	Eligible Patients Efficacy Rate	95% C.I.*
Study 1	Gatifloxacin	71% (94/132)	(-15.7%, 8.4%)	63% (95/152)	(-18.1%, 8.2%)
	Levofloxacin	75% (99/132)		67% (100/149)	
Study 20	Gatifloxacin	58% (76/132)	(-24.91%, 24.87%)	55% (78/140)	(-23.4%, 23.21%)
	Cefuroxime	58% (73/127)		55% (78/140)	

*95% Confidence Interval around the difference in cure rates.

In line with the recent July 1998 Anti-infective Advisory Committee meeting, the limit of equivalence will be considered independent of the observed response. Since 15% was discussed and agreed upon by the FDA in reference to all recently submitted gatifloxacin protocols, 15% will be used in determining equivalence studies 1 and 20. For study 1, cure rates were slightly higher for levofloxacin across all analyses. The lower limit of the 95% CI for the 4 analyses is within or slightly beyond the designated limit of –15%. For study 20, cure rates were equal or slightly higher for gatifloxacin. The 95% CI for the difference in cure rates were narrow but widened when patients who were improved were considered as failures, and the lower limit exceeded –15%.

Additional analyses by gender, race and age were performed by the applicant. Race analyses showed that Black and Hispanic subjects had higher cure rates than White

subjects in both gatifloxacin and comparator arms, but the number of non-White patients was small compared to White patients. Gender analyses did not show a meaningful difference between males and females in either arm, and age analyses showed higher cure rates in both arms in patients below age 65 compared to those 65-74 years old and those older than 75, but again the number of patients in the latter 2 groups was small compared to those in the <65 group.

Results of studies 1 and 20 show that patients who were current smokers at study entry had a higher cure rate than those who were not, both in the gatifloxacin arm and the comparator arm (a patient was considered a current smoker if he or she was a smoker at the time of enrollment or had stopped smoking within the two months before enrollment). To find out if other variables accounted for this difference in response rates, logistic regression analyses were performed for current smoking status and history of smoking on the clinical response using the following covariates: age, race, gender, history of asthma, use of other drugs concomitantly and the presence of one of the 5 major pathogens isolated. The analyses did not identify any significant imbalance between the various treatment groups that would explain the observed effect of current smoking status on the overall outcome. Its importance as a prognostic variable remains questionable.

Bacteriologic Response

Bacteriologic response rates are shown in tables 7 and 8. The reviewer's analysis considered ineligible those patients who had >10 epithelial cells/LPF in their sputum and, for those patients whose 3 major symptoms of cough, dyspnea and sputum production did not return to baseline at the TOC visit or the extended follow-up visit, the organism was classified as persisted unless it was classified as eradicated through a follow-up culture.

Table 7 **Bacteriologic Eradication Rates of Gatifloxacin by Pathogen, Microbiologically Evaluable Patients, All 3 Studies (N=439)**

	Number Eradicated/Number Isolated (%)			
Pathogen	Applicant's analysis		Reviewer's analysis	
H. influenzae	75/78	(96)	65/77	(84)
M. catarrhalis	65/71	(92)	55/68	(81)
H. parainfluenzae	27/32	(84)	23/29	(79)
S. aureus	42/46	(91)	31/39	(79)
S. pneumoniae	33/33	(100)	29/32	(91)
Penicillin Sensitive	23/23	(100)	N/A	N/A
Penicillin Intermediate	7/7	(100)	N/A	N/A
Penicillin Resistant	2/2	(100)	N/A	N/A
Penicillin Sensitivity Unknown	1/1	(100)	N/A	N/A

Table 8 **Bacteriologic Eradication Rates by Pathogen, Microbiologically Evaluable Patients, Studies 1 and 20, Reviewer's analysis**

	Number Eradicated/Number Isolated (%)							
	Study 1				Study 20			
Pathogen	Gatifloxacin		Levofloxacin		Gatifloxacin		Cefuroxime	
H. influenzae	21/25	(84)	18/19	(95)	12/20	(60)	10/22	(45)
M. catarrhalis	29/33	(88)	20/26	(77)	14/23	(61)	5/9	(56)
H. parainfluenzae	10/13	(77)	13/19	(68)	4/6	(67)	3/5	(60)
S. pneumoniae	12/13	(92)	14/16	(87)	6/8	(75)	5/9	(56)
S. aureus	14/21	(66)	18/20	(90)	5/6	(84)	7/9	(78)

The applicant's data and the reviewer's analyses show acceptable efficacy over the 5 most frequently isolated pathogens. However, most of the organisms in these studies were presumed eradicated based on clinical data and not actually shown to be eradicated through sputum cultures. The number of Penicillin-Resistant *S. Pneumoniae* was insufficient to assess efficacy against those organisms. Of 9 Penicillin-Intermediate or Resistant S. Pneumoniae, only one was confirmed eradicated (Penicillin-Intermediate) and the remaining 8 were presumed eradicated. Since the role of S. aureus in AECB is not entirely clear, a closer look at patients with this organism in the open-label study and in the gatifloxacin group of the two controlled studies showed that 22 patients had a pure growth of S. aureus in all studies combined, 19 of which had a bacteriological eradication (17 were presumed and 2 confirmed).

V. Adverse Events

Drug-related adverse events occurred in 19%, 34% and 30% of patients on gatifloxacin in studies 4, 1 and 20 respectively. Patients on comparator drugs had a slightly lower incidence: 28% and 23% in studies 1 and 20 respectively. Most adverse events in the gatifloxacin group were mild to moderate and non-serious in nature. The most common were nausea, vaginitis, diarrhea, dizziness, vomiting, headache and abdominal pain. Class-related events, namely phototoxicity, tendinitis, and seizures, were not encountered. From these studies, it appears that gatifloxacin has a favorable clinical adverse event profile.

Serious adverse events in patients on gatifloxacin included one case each of congestive heart failure, atrial fibrillation, syncope, nausea, abdominal pain, vomiting, bronchitis, COPD exacerbation, dyspnea, accidental injury, testicular cancer, arm and back pain, hospitalization for severe AECB, lung cancer and pneumonia. There were 2 events each of dyspnea, syncope and asthma and 3 events of myocardial infarction. There were 3 deaths reported in the gatifloxacin arms and none in the comparator arms. One patient died of COPD and 2 of myocardial infarction. None of the deaths or serious adverse events was attributed to study medication by the investigator.

From these studies, it appears that gatifloxacin has a favorable clinical adverse event profile.

VI. Laboratory Abnormalities

In patients with normal pre-treatment laboratory values, the abnormalities that did occur were usually mild. The most significant were hyperglycemia (11% of 47 tested), anemia (7% of 454 tested), elevated BUN (6% of 507 tested), elevated AST (6% of 464 tested), elevated ALT (6% of 479 tested), elevated total bilirubin (3% of 505 tested), decreased bicarbonate (13% of 335 tested), hypernatremia (7% of 474 tested) and neutropenia (5% of 504 tested). For comparison, in patients in the comparator arms, elevated AST occurred in 5% of 284 tested, elevated ALT in 5% of 295 tested, elevated bilirubin in 2% of 310 tested, , elevated BUN in 6% of 303 tested, hyperglycemia in 10% of 30 tested, anemia in 13% of 273 tested, and neutropenia in 3% of 303 tested. In the gatifloxacin arms, a total of 12 patients had an elevation of both AST and ALT, 2 of them had an elevated Alkaline Phosphatase and one had an elevated bilirubin to 1.3 mg/dl. Hyperglycemia occurred in 11% of the patients. Blood sugar levels did not rise beyond 132 mg/dl.
In patients who had abnormal (Grade 1, 2 or 3) pre-treatment laboratory values, there was occasional worsening to a higher grade during or post-treatment. AST and ALT worsened to Grade 3 on Day +9 in a patient later discovered to have testicular cancer. There was one case of bilirubin elevation from grade 2 to grade 3, one case of neutropenia from grade 1 to grade 3, and one case of hypernatremia from grade 1 to grade 3. One patient experienced a Grade 4 hyponatremia to 114 mEq/dl, pre-treatment level being 130 mEq/dl.

Laboratory abnormalities to be examined more closely in the review of the integrated safety summary are hyperglycemia, anemia, bicarbonate abnormalities, hypernatremia and liver enzyme elevations.

VII. Conclusion

From the review of the above studies, gatifloxacin seems to have similar efficacy to the comparators. Efficacy rates were somewhat lower than those of levofloxacin but at least equal to those of cefuroxime. Microbiological efficacy was demonstrated for patients with baseline sputum cultures positive for one the 5 major organisms isolated (*H. influenzae, S. pneumoniae, M. catarrhalis, S. aureus* and *H. parainfluenzae),* but most of these were presumed eradicated based on clinical outcome. The safety profile seemed favorable but should be assessed further through the review of the integrated safety summary.

Given that the clinical data are not very robust, and given that AECB is a clinical diagnosis with an outcome assessment that is mostly subjective, it is recommended that the request for approval of gatifloxacin for this indication be examined further in light of the results of other studies submitted to this NDA for the indication of community-acquired pneumonia. If data are in favor of approval for the latter indication, it is the

reviewer's recommendation that approval for AECB be granted for *H. influenzae, S. pneumoniae, M. catarrhalis, S. aureus and H. parainfluenzae*. The applicant also requested that approval be granted for *K. pneumoniae* and *E. cloacae*. While the eradication rates were high (90% for *K. pneumoniae* and 80% for *E. cloacae*), the total number of organisms isolated is insufficient to recommend approval for these 2 organisms. Similarly, there were not enough penicillin-resistant *S. pneumoniae* isolated to include that subset in the label.

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Review of Individual Trials

8.2.1 Trial #1

Applicant's Study AI420-004: An Open-Label Multicenter Non-Comparative Study of Oral Gatifloxacin In The Treatment of Acute Exacerbation of Chronic Bronchitis.

8.2.1.1 Rationale/Objective

The objectives of the study were to establish the clinical and bacteriologic efficacy of gatifloxacin at a dose of 400 mg orally once a day (QD) in the treatment of AECB, and evaluate the safety profile of gatifloxacin at 400 mg QD in this population.

8.2.1.2 Design

This was an open-label, multicenter study designed to assess the safety and efficacy of gatifloxacin given orally at a dose of 400 mg once daily for ten days in the treatment of adult patients with AECB. Seventeen investigators were recruited in the US. The planned enrollment was 200 patients. This sample size was expected to include a sufficient number of patients with infections caused by *S. pneumoniae*. In addition, with 200 patients evaluable for safety, the incidence of an adverse clinical event could be estimated with a standard error of no more than 3% (assuming the incidence was less than 20%).

Reviewer's comments: *This trial is a phase II study designed to provide a preliminary idea about the safety and efficacy of gatifloxacin in the treatment of AECB. Since this is an open-label, non comparative trial, efficacy results have only a supportive value to other comparative trials designed to establish equivalence of gatifloxacin to drugs approved for the indication of AECB.*

8.2.1.3 Protocol

8.2.1.3.1 Population

For inclusion, patients with a history of chronic bronchitis (i.e., productive cough on most days for at least three consecutive months in two consecutive years) and a diagnosis of AECB had to meet all of the following criteria:

- Eighteen years of age or older;
- Clinical diagnosis of acute exacerbation of chronic bronchitis, defined as:
  - The presence of purulent sputum confirmed by Gram stain examination [>25 polymorphonuclear leukocytes (PMN) and <10 squamous epithelial cells (epi) per low power field (LPF)];

  - The presence of at least two of the following signs and symptoms:
    - increased cough and/or dyspnea;
    - increased sputum volume;
    - increased sputum purulence.
- For women of childbearing potential:
  - A negative urine pregnancy test within two days prior to enrollment;
  - Commitment to use an effective method of contraception from the start of gatifloxacin treatment until the end of their participation in the study;
- Written informed consent (from patients or their guardians) before any study procedures were performed.

Patients were excluded if they met any of the following criteria:

- Pregnant or lactating;
- History of significant hypersensitivity reaction to any fluoroquinolone compound;
- Received a systemic antibiotic therapy within seven days prior to enrollment, or were likely to require other systemic antibiotic(s) concomitantly;
- Diagnosis of pneumonia confirmed by the presence of pulmonary infiltrates on a chest x-ray;
- Previously diagnosed disease(s) of immune function (e.g., AIDS or history of clinical manifestations of HIV infection, neutrophil count $<1000/mm^3$);
- Previously diagnosed condition that would tend to mimic or complicate the course and evaluation of the infectious process;
- Known renal insufficiency (i.e., serum creatinine ≥1.5 mg/dL or requiring renal dialysis);
- Current clinically significant hepatic disease (i.e., aspartate amino transferase (AST) and/or alanine amino transferase (ALT) and/or total bilirubin ≥3 times the upper limit of normal);
- Malabsorption syndromes or other gastrointestinal disturbances that would affect drug absorption;
- Previous treatment in any gatifloxacin study.

Reviewer's comments: *Inclusion and exclusion criteria were appropriate and clearly identified prior to initiation of the study. The exclusion of patients with AIDS, renal insufficiency and hepatic disease makes it difficult to predict safety and efficacy in these population groups.*

Exacerbation type at entry was determined according to the following criteria established by Anthonisen, et al.

- Type I - increased dyspnea, increased sputum volume and increased sputum purulence;
- Type II - any two of the three symptoms of Type I;
- Type III - any one of the three symptoms of Type I.

Patients received gatifloxacin 400 mg orally once a day for 10 days. Adjunctive medications such as bronchodilators and intranasal or systemic steroids were permitted as needed. Patients were also permitted to receive supportive non-drug therapies (e.g., postural drainage, oxygen) at the discretion of the Investigator. Patients were not to receive any other systemic antibiotic therapy from 7 days prior to enrollment until completion of the extended follow-up assessment. Investigators were permitted to discontinue study drug and remove patients from the study for the following reasons:

- An adverse event;
- Persistence or worsening of signs and symptoms of the acute infection after 3 days of gatifloxacin therapy;
- An intercurrent illness;
- Patient's decision not to participate any further;
- Investigator's decision that discontinuation was in the patient's best interest;
- A female patient with a positive pregnancy test during gatifloxacin therapy (immediate discontinuation);
- Decision of the sponsor to terminate the study (at some or all sites).

Patients with one or more gatifloxacin-resistant pre-treatment pathogens were removed from the study if the investigator felt it was in their best interest. Patients whose condition had not improved or had worsened after three days of study drug therapy (early treatment failures) were to be removed from the study and to have the same clinical and laboratory procedures performed as those specified for the post-treatment visit scheduled for Day +7 to Day +14 before starting alternative antibiotic therapy.
Patients were seen by Investigators pre-treatment (within 2 days before the start of dosing), during treatment (Day 3 to Day 5, inclusive) and post-treatment (Day +7 to Day +14, inclusive) (Table 1). They were also contacted once by phone at the end of treatment (Day +1 to Day +3, inclusive) and once three to four weeks post-treatment (Day +21 to Day +28, inclusive). At the end-of-treatment telephone contact, if the patient's signs and symptoms had not returned to baseline, or if clear clinical improvement had not occurred, the patient returned to the office/clinic to undergo the procedures specified for the Day +7 to Day +14 post–treatment visit. At the extended follow-up telephone contact, if increased sputum production persisted, or recurred after

initial improvement, the patient returned for further evaluation, including sputum assessment and culture, if purulent.

Table 1 Study Procedures

Procedure	Pre-treatment (Within 2 days prior to dosing)	During Treatment (Days 3 to 5)	End of Treatment [a] (Days +1 to +3)	Post-Treatment (Days + 7 to +14)	Extended Follow-up[a] (Days + 21 to +28)
Screening	X	-	-	-	-
Chest X-Ray	X	X[b]	-	X[b]	-
Medical History	X	-	-	-	-
Physical Exam	X	-	-	X	-
Vital Signs	X	X	-	X	-
Clinical Evaluation	X	X	X	X	X[d]
Pulmonary Function Tests	X	-	-	X	-
Laboratory Tests	X	X[c]	-	X	-
Sputum Smear	X	X	-	X	X[d]
Sputum Assessment	X	X	-	X	X[d]
Sputum Culture	X	X	-	X	X[d]
Assess Adverse Events	-	X	X	X	X
Assess Medication Use	-	X	X	X	-
Pregnancy Test	X	-	-	X	-

a Telephone contact. If patient not clinically improved, office visit to be scheduled for further evaluation.
b If clinically indicated.
c Could include one or two blood samples for pharmacokinetic analysis.
d Office visit to be scheduled for further evaluation if increased sputum production persisted. Culture to be done if purulent sputum specimen obtained.

All laboratory procedures, including appropriate cultures, were performed by local laboratories. Some Investigators performed Gram stain procedures on site to expedite determination of sputum purulence and, therefore, patient eligibility. In those cases, the additional Gram stains performed at the local laboratories served as confirmatory tests.

All pre-treatment sputum specimens found purulent (>25 PMN and <10 epi per LPF) on the preliminary smear were plated semi-quantitatively for aerobic growth, and all potential pathogens isolated were tested for study drug susceptibility. Pulmonary function was measured by spirometer, including determination of the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC). Oxygen saturation was measured by pulse oximetry. Hematology, serum chemistry, and urinalysis tests

included: White blood cell count (WBC) with differential, hemoglobin, hematocrit, platelet count, AST, ALT, total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, glucose, amylase, sodium, potassium, chloride, bicarbonate, qualitative urinalysis, microscopic urinalysis. A urine pregnancy test was performed on all women of childbearing potential. Positive urine pregnancy tests were confirmed with a serum-based pregnancy test.

Patients were observed at least once during treatment (between Day 3 and Day 5, inclusive), and as frequently as deemed necessary by the investigator. If a sputum specimen was produced during this visit, purulence was assessed and, if purulent, the specimen was plated for aerobic growth. A chest x-ray was taken if clinically indicated.

In the three-day period immediately following the end of therapy (i.e., Day +1 to Day +3, inclusive), patients were contacted by telephone and queried about the clinical signs and symptoms of infection, the occurrence of adverse events, and compliance with the dosing regimen. If a patient's signs and symptoms had not returned to baseline, or if clear clinical improvement had not occurred, the patient was scheduled for an immediate office visit.

Between Day +7 and Day +14, patients were evaluated in the office/clinic for clinical and bacteriologic response to study drug therapy and the occurrence of adverse clinical events. If a patient was still producing sputum, a specimen was obtained for assessment of purulence, quantitative culture and susceptibility testing. If a laboratory test result became abnormal or worsened from an abnormal pre-treatment level, the test was repeated at appropriate intervals until the value either returned to the pre-treatment level or stabilized.

Patients who had a satisfactory clinical response were contacted by telephone approximately two weeks later (Day +21 to Day +28) to assess relapse of the acute infection. Patients were queried as to the presence and severity of clinical signs and symptoms of infection, ingestion of any antibiotics since the last office/clinic visit, and occurrence of adverse clinical events.

If increased sputum production persisted, or recurred after initial improvement, an office/clinic visit was scheduled for further evaluation. This included collection of a sputum sample for assessment of appearance and evaluation of a Gram-stained smear; if the specimen was purulent, bacteriologic culture and susceptibility testing of any isolated pathogens were performed.

Reviewer's comments: *Patient monitoring was adequate in terms of frequency of visits and phone check-ups. Laboratory tests were also adequate for proper detection of toxicity. Study drug levels were not measured to verify compliance, which was only done through a patient maintained diary.*

8.2.1.3.2 Endpoints

Clinical and bacteriologic responses were determined from data at the Test of Cure (TOC) visit scheduled between Day +7 and Day +14, inclusive. In the analysis, due to potential schedule conflicts, any visit from Day +5 to Day +18, inclusive, was acceptable. Treatment failures could be assessed at any time prior to Day +18, but patients had to receive a minimum of 3 days of therapy.

Reviewer's comments: *The test of cure window of +7 to +14 days was expanded to +5 to +18 days. This was done to allow for any difficulties in the patient scheduling an office visit. This change was made with the understanding that the lower value of the TOC window would still be greater than 5 half-lives of gatifloxacin, and it was done prior to datalock and unblinding of the study. This expansion did not affect the interpretation of the study results.*

Investigators assigned a clinical response to each patient and a bacteriologic response to each pre-treatment pathogen.

Clinical Response

Each patient was assigned a clinical response of Cured, Improved, Unsatisfactory, or Unable to Determine (UTD). For analysis, responses of Cured and Improved were categorized as Satisfactory.

CURED:

- All signs and symptoms related to the acute infection (cough, dyspnea, sputum production, and sputum purulence) returned to the patient's pre-infection level; and
- No new signs or symptoms of acute infection were present; and
- If present at study entry, fever was resolved (i.e., temperature ≤38°C).

IMPROVED:

- All signs and symptoms related to the acute infection (cough, dyspnea, sputum production, and sputum purulence) were, at a minimum, improved, but not all were restored to the patient's pre-infection level; and
- No new clinical signs and symptoms of acute infection were present; and
- If present at study entry, fever was resolved (i.e., temperature ≤38°C).

UNSATISFACTORY:

- Signs and symptoms related to the acute infection (cough, dyspnea, sputum production, or sputum purulence) did not improve; or
- New clinical signs and symptoms of acute infection were present; or
- If present at study entry, fever persisted (i.e., temperature >38°C); or